SOD mimetic Copper Complexes

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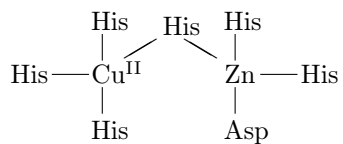
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Review

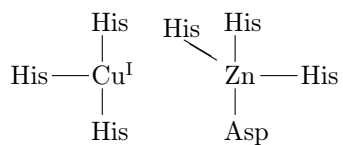## 1 Copper protein SOD

Superoxide dismutase (SOD) Cu–Zn active center.[14]
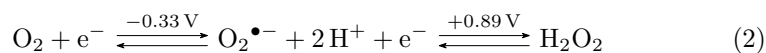
$$\text{His} \quad \text{His} \quad \text{His}$$

His—Cu^{II} Zn—His

His   Asp

1a

Asp = aspartate

His = histidine

His   His   His

His—Cu^{I} Zn—His
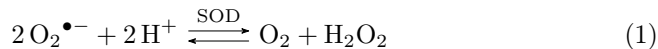
His   Asp

1b

Superoxide dismutases catalyze the proton-dependent dismutation of two superoxide radical anions to molecular oxygen and hydrogen peroxide.

$$2\,O_2{}^{\bullet-} + 2\,H^+ \underset{\longleftarrow}{\overset{SOD}{\longrightarrow}} O_2 + H_2O_2 \tag{1}$$

$$O_2 + e^- \underset{\longleftarrow}{\overset{-0.33\,V}{\longrightarrow}} O_2{}^{\bullet-} + 2\,H^+ + e^- \underset{\longleftarrow}{\overset{+0.89\,V}{\longrightarrow}} H_2O_2 \tag{2}$$

[1]

[8, p.76]

Table 1: Rate constants of superoxide dismutation (without SOD)

Reaction	k, $M^{-1}s^{-1}$
$O_2{}^{\bullet-} + O_2{}^{\bullet-}$	6
$O_2{}^{\bullet-} + HO_2{}^{\bullet}$	1.5×10^7
$HO_2{}^{\bullet} + HO_2{}^{\bullet}$	7.6×10^5

[2]

[4, p.8]

Fact. $[O_2{}^{\bullet-}]$ = 10^{-11} M (molarity in organism).

Fact. [SOD] = ca. 10^{-5} M (molarity in organism).

The dismutation of superoxide without catalyst is a second-order reaction, depending on the concentration of superoxide.(Table 1) Since the superoxide concentration in organisms is very low, the dismutation rate is also low. This causes damage of the DNA. Catalyst SOD is present in large excess, so the reaction kinetics is pseudo first-order.[4, p.9] The SOD-catalyzed dismutation of superoxide is the fastest enzymatic reaction and proceeds at a near diffusion-limited rate (k = 2×10^9 $M^{-1}s^{-1}$, 298 K).[6, p.204]

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[1] NHE, pH = 7.

[2] $O_2{}^{\bullet-} \underset{-H^+}{\overset{H^+}{\rightleftarrows}} HO_2{}^{\bullet}$, pK_a = 4.88.

Table 2: Bond distances

		X-ray O–O, Å
O_2	Oxygen	1.21
$O_2{}^{\bullet-}$	Superoxide	1.33
$O_2{}^{2-}$	Peroxide	1.49

[3]

[4, p.7]

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[3] Hydrogen peroxide: O–O–H angle: $102.7\pm0.3°$

2 Model Complexes
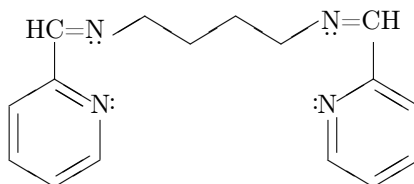
2a

2a = 1-pyridin-2-yl-N-[4-(pyridin-2-ylmethylideneamino)butyl]methanimine

◇ $[Cu^{II}\mathbf{2a}][ClO_4]_2$ [11]

◇ $[\{Cu^I\mathbf{2a}\}_2][ClO_4]_2$ [11]

## 2.1 Spectral Properties

Table 3: UV/Vis of Model Complex

Complex		λ, nm (ε, M^{-1}cm^{-1})	color
$[Cu^I\mathbf{2a}]_2{}^{2+}$	Dimer	478 (13600)	brown
$[Cu^I\mathbf{2a}]^+$	Monomer	422 (3700) / 596 (2400)	green
$[Cu^{II}\mathbf{2a}]^{2+}$	Monomer	710 (110)	blue

Remark. $[Cu^I\mathbf{2a}]_2{}^{2+}$ shows spectra independent from the solvent. $\Rightarrow$ No participation of the solvent to the inner coordination sphere. The peak at 478 nm can be assigned to a ligand to metal charge transfer (LMCT).

Remark. $[Cu^I\mathbf{2a}]^+$ is sensitive to the solvent. $\Rightarrow$ Participation of the solvent to the inner coordination sphere of Cu^I.[11, p.3346][5, p.1706]
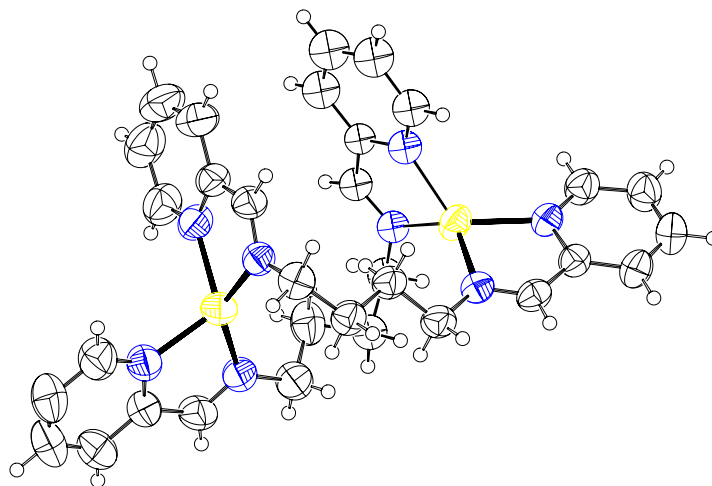
Remark. $[Cu^{II}\mathbf{2a}]^{2+}$ tends to become five-coordinate.[11, p.3342]

2.2   Structures
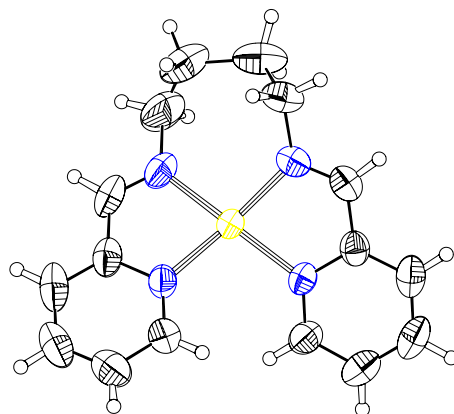
blue

Figure 1: $[Cu^{II}2a]^{2+}$, Copper (II) Monomer, distorted square planar coordination (dihedral angle: 33.0°), *CCDC 148873*

brown

Figure 2: $[Cu^{I}2a]_2{}^{2+}$, Copper (I) Dimer, tetrahedral coordination (dihedral angle: 89.6°), Cu–Cu: 5.86 Å, *CCDC 148874*

Remark. Double-helical architecture, self-assembly.[13]

2.3   Copper(I) Dimer/Monomer equilibrium

The copper(I) complex is dimeric. The coordination geometry of the N_4 donor system is tetrahedral (Figure 2). The coordination of superoxide seems to be impossible for this coordination geometry.

$$\text{Dimer} \; \underset{}{\overset{K}{\rightleftharpoons}} \; 2 \; \text{Monomer}$$
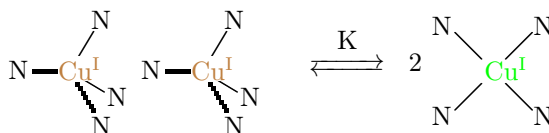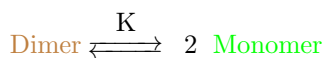
$$K = \frac{k_M}{k_D} \tag{3}$$

The dimeric copper(I) complex dissociates to two monomeric copper(I) complexes.[4] The monomeric copper(I) complex and the corresponding monomeric copper(II) complex are the reactive components for the dismutation. Because of the rigid structure of the ligand **2a**, the monomeric copper(I) complex is probably coordinated distorted square-planar, similar to the copper(II) complex. The superoxide is able to attack.

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[4] An example for the structure of a related monomeric copper(I) complex is shown in [2]. The dihedral angle is 50.6°.

2.4 Electron Transfer Reaction
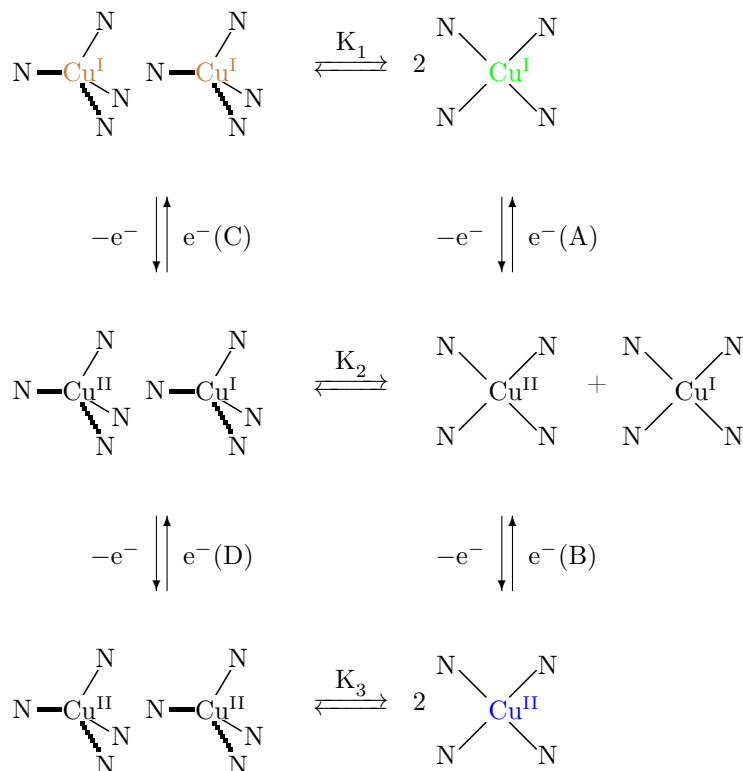
Scheme 1: Reaction mechanism

$(A) = (B)$

Remark. Equilibrium K_1 (Equation 3) is the dominant path and rate determining (slow) step in the reduction reaction. The reason is the major rearrangement of the ligand **2a**.
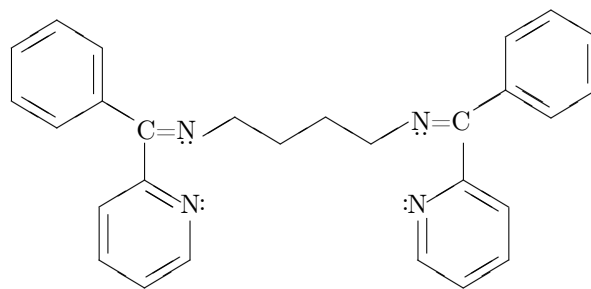
2.5   SOD mimetic activity

Table 4: Activity – Tetrahedral distortion

Complex	Activity, %	Dihedral angle, °
$[Cu^{II}\mathbf{2a}][ClO_4]_2$	1.5	33.0
$[Cu^{II}\mathbf{2b}][ClO_4]_2$	3.0	29.5
$[Cu^{II}\mathbf{2c}][ClO_4]_2$	0.3	
$[\{Cu^{I}\mathbf{2c}\}_2][ClO_4]_2$	0.3	

[5]

[12]

2b
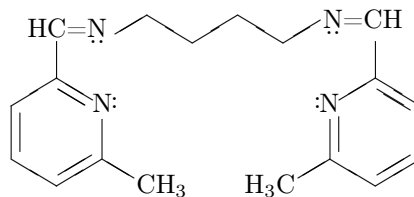
2c

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[5] In % of SOD activity.

Remark. Ligand **2b** is more rigid than **2a**. The positive mesomeric effect (+M) of the phenyl group might play a considerable role. The tetrahedral distortion of the N_4 system is smaller (Ligand planarity). The monomeric copper(I) complex of **2b** is probably a more redox-reactive intermediate, explaining the higher SOD mimetic activity.

Remark. Ligand **2c** stabilizes the less redox-reactive tetrahedral coordinated dimeric copper(I) complex, because of steric reasons caused by the two methyl groups. The complex shows a lower SOD mimetic activity. Using the monomeric copper(II) or the dimeric copper(I) complex as scavenger has no influence on activity (See Table 4).

Claim. More rigid square planar monomeric copper systems with smaller N_4 torsion angles should show higher SOD mimetic activity. But these systems tend to build stable higher supramolecular structures, like double-helical, triangular, and square [2x2] grid complexes.[13][15][9]
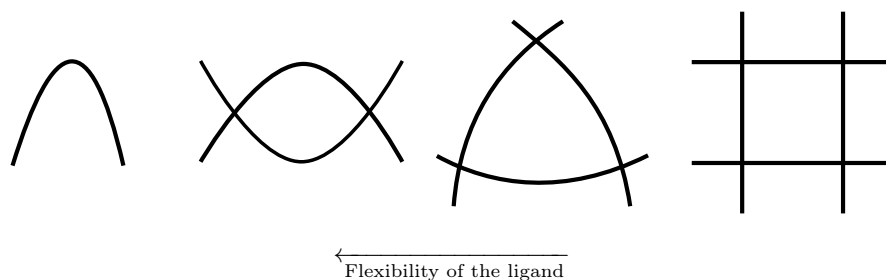

Flexibility of the ligand

Figure 3: monomer, double-helical, triangular and square [2x2] grid copper(I) complexes

Conjecture. *Equilibrium of flexible copper(I) species in solution.*

$$\text{Monomer} \xrightleftharpoons{K_1} \text{Dimer} \xrightleftharpoons{K_2} \text{Trimer} \xrightleftharpoons{K_3} \text{Tetramer} \qquad (4)$$

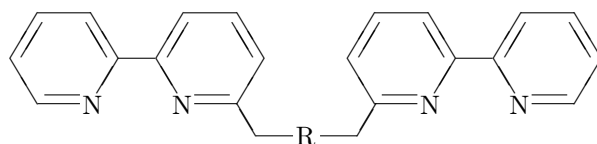[6]

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[6] Monomer is the reactive species for the dismutation.

2.6 Promising SOD mimetic complexes

◇ Copper complexes with flexible bis(bipyridine)-based or oligobipyridine ligands, that build double-helical architecture and redox-reactive monomeric N_4 copper(I) species in equilibrium.[13][5]

3

◇ Copper complexes with Schiff base ligands, that enforce redox-reactive square planar coordination of monomer copper(I), because of geometric constraints. Type of ligand **2d**.[7][3][1]
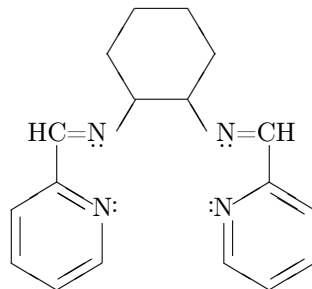
2d

2d = N,N'-bis(pyridine-2-ylmethylene)-(S,S)-1,2-cyclohexanediamine

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[7] The dihedral angle of the copper(II) complex of **2d** is 9.1°.[3]

3   Copper-Oxygen complexes

Conjecture. *copper(II)-dioxygen species*

1. $O_2 \longrightarrow$ mononuclear copper(II)-superoxo, *end on*

2. $O_2 \longrightarrow$ mononuclear copper(II)-superoxo, *side on*

3. $O_2 \longrightarrow$ dinuclear copper(II)-peroxo, *end on/end on*

4. $O_2 \longrightarrow$ dinuclear copper(II)-peroxo. *side on/side on*

5. $O_2{}^{\bullet-} \longrightarrow$ mononuclear copper(II)-peroxo, *end on*

6. $O_2{}^{\bullet-} \longrightarrow$ mononuclear copper(II)-peroxo, *side on*

Example 1. mononuclear copper(II)-superoxo (1.), N_4 donor.

$[(\mathbf{TMG_3tren})\mathbf{Cu^{II}\!-\!O\!-\!O^\bullet}]^+$ SCHINDLER [16]

1. X-ray

   (a) O–O distance: 1.280(3) Å
   (b) O–O–Cu angle: 123.53(18)°
   (c) Color: green

2. UV/Vis

   (a) $\lambda = 442$ / 690 nm
   (b) copper(I) complex: »colorless«

3. IR, Raman

   (a) $\tilde{\nu}_{O-O} = 1122$ cm^{-1}

The superoxide ($O_2{}^{\bullet-}$) is coordinated *end-on.*
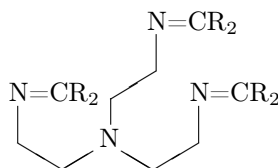
4

4 = Tris(tetramethylguanidino)tren (TMG$_3$tren)

Example 2. binuclear copper(II)-peroxo (3.), N_4 donor.

[[(Tris(2-pyridylmethyl)amine)Cu^{II}]$_2$(O$_2$)]$^{2+}$ KARLIN [7]

1. X-ray

    (a) O–O distance: 1.432(6) Å
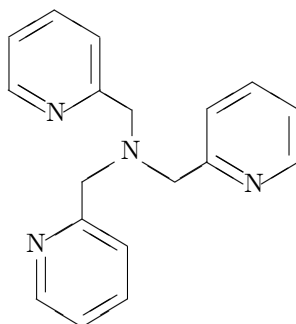   (b) O–O–Cu angle: 107.7(2)°
    (c) Cu–Cu: 4.359(1) Å

2. UV/Vis

    (a) $\lambda = 530$ (10000) / 600sh (6000) nm

3. IR, Raman

    (a) $\tilde{\nu}_{O-O} = 832$ cm^{-1}

The peroxide ($O_2{}^{2-}$) is coordinated *end on/end on.*

5

5 = Tris(2-pyridylmethyl)amine (tmpa)

IUPAC 1-pyridin-2-yl-N,N-bis(pyridin-2-ylmethyl)methanamine

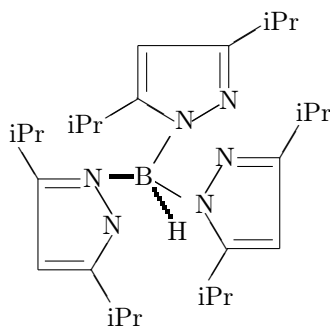**Example 3.** binuclear copper(II)-peroxo (4.), N_3 donor.

$[(HB(3,5-iPr_2pz)_3Cu^{II}]_2(O_2)$ Kitajima [10]

iPr = isopropyl

pz = pyrazolyl

1. X-ray

    (a) O–O distance: 1.412 Å
    (b) Cu–Cu distance: 3.56 Å

2. UV/Vis

    (a) λ = 449 (21000) / 551 (790) nm

3. IR, Raman

    (a) $\tilde{\nu}_{O-O}$ = 741 cm^{-1}

The peroxide $(O_2{}^{2-})$ is coordinated *side on/side on*.

6

6 = »hydrotris(pyrazolyl)borate«

Claim. There is no evidence for the participation of a copper(II)-oxygen complex in the mechanism of the dismutation of superoxide catalyzed by the model complex.

References

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